

# GOPEN ACCESS

**Citation:** Espinós U, Fernández-Abascal EG, Ovejero M, Lahera G (2021) Social cognition in first-degree relatives of bipolar disorder: Theory of Mind and nonverbal sensitivity. PLoS ONE 16(3): e0246908. https://doi.org/10.1371/journal. pone.0246908

**Editor:** Zezhi Li, National Institutes of Health, UNITED STATES

Received: September 24, 2020

Accepted: January 27, 2021

Published: March 2, 2021

**Copyright:** © 2021 Espinós et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** The authors recceived no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

**RESEARCH ARTICLE** 

# Social cognition in first-degree relatives of bipolar disorder: Theory of Mind and nonverbal sensitivity

# Usue Espinós<sup>1</sup>\*, Enrique G. Fernández-Abascal<sup>1</sup>, Mercedes Ovejero<sup>2</sup>, Guillermo Lahera<sup>3</sup>

1 Facultad de Psicología, Universidad Nacional de Educación a Distancia, Madrid, Spain, 2 Facultad de Psicología, Universidad Complutense de Madrid, Madrid, Spain, 3 Facultad de Medicina, Universidad de Alcalá de Henares, Madrid, Spain

\* usueespinos@asocbipolar.com

# Abstract

Social cognition might be impaired in first degree relatives (FDR) of BD but existing research shows controversial results about social cognitive impairments in this population. The aim of this study was to assess Theory of Mind (ToM) and nonverbal sensitivity in FDR of BD and compare the results with those of two groups of persons with remitted bipolar disorder (BD), type I and II, and a control group. Social cognitive ability was examined in first degree relatives of BD, with a biological parent, offspring or sibling diagnosed with the disorder. For this study, 37 FDRs of bipolar patients, 37 BD I, 40 BD II and 40 control participants were recruited. Social cognition was explored by means of the Reading the Mind in the Eyes Test and the MiniPONS. Results showed a significant impairment in FDR of BD in the ToM task, but not in nonverbal sensitivity. Performance of FDRs in social cognition is better than that of BDs (either type I or type II) but worse when compared with that of healthy individuals without a family history of psychiatric disorders. Nevertheless, no differences were found between BD I and BD II groups. Males and older participants showed a worse performance in all groups. Group family therapy with FDRs of BD might include training in the recognition of nonverbal cues, which might increase the understanding of their familiars with BD, in order to modify communication abilities.

# Introduction

Bipolar disorder (BD) is a psychiatric condition, characterized by extreme fluctuations in energy and mood [1]. Bipolar II (BD II) is distinguished from bipolar I (BD I) by the presence of hypomanic episodes, and is a milder condition than BD I, in relation with mood elevation [1]. With respect to the severity, for some authors, psychosocial impairment increases significantly in BD I with most increments in manic symptom severity [2]. Few studies have compared BD II with healthy controls, but findings suggest that BD II patients are at least so functionally disabled as BD I patients, and experience functional impairment in all domains, that continues after remission of symptoms [3]. Nevertheless, with regard to research on psychosocial functioning, BD II is not only understudied, but there is also scarce evidence about this question. Most research evaluating functional disability in BD is based on patients with BD I, with no comparison of the two groups, BD I and BD II [4, 5].

Social impairment can be observed in many BDs [6]. Evidence suggests that during euthymic periods, they also undergo interpersonal difficulties [7]. It is estimated that up to 60% of individuals do not fully recover after episodes [8] and only 38% of them achieve functional recovery after a manic phase [9]. BD can be profoundly disabling, and is associated with a substantial loss of work performance, and the consequent financial burden [10]. In relation with severity of BD, a lack of objectivity exists in the current diagnostic system to differentiate more severe patients. Some studies define severity of illness course as early onset of BD [11]; other authors consider illness severity of BD as having anxiety symptoms [12, 13], or correlation with familial psychiatric history: in most cases, with a first-degree relative with severe mental disorder [14, 15].

There is evidence indicating that social cognition deficits are present in patients with BD, even in the euthymic phase [16]. BD patients exhibit deficits in several social cognition domains, including emotional processing [17]. Social cognition refers to the psychological operations related to the perception and interpretation of social signals, that enable individuals to learn about the world, oneself, and the others [18]. A central process within this construct is Theory of Mind (ToM), defined as -the competence to interpret and predict other persons' behavior by attributing mental states such as feelings, desires, beliefs, opinions and intentions, and the ability to share and recognize the emotions of others, to understand and predict their behavior [19]. There are divergent findings in social cognition studies of BD. Some studies found worse performance in BD I compared to BD II [20]. For other authors, both groups have a similar poor performance in social cognition tasks, compared to controls [21, 22]. Social cognition has been mostly investigated with BD through a ToM measure, the "Reading the Mind in the Eyes Test" (RMET) [23]. Many authors have found deficiencies in this population; remitted bipolar participants, when assessed with this tool, scored significantly lower, when compared to healthy controls [24–27].

Another aspect of social cognition is nonverbal sensitivity, that is, the ability to decode affective nonverbal cues in others [28]. One example of nonverbal sensitivity measure is the test MiniPONS [29], a test with ecological validity, which includes fundamental information such as movements of face, body and voice. This test presents scenes that are nearer to real life situations than static pictures. Expression of emotion through body language has not been extensively explored [30], as communication of emotions by means of dynamic body movements and gestures conveys specific information about emotion processing of others' emotional states and intentions [31]. Variables such as age and gender differences have also been investigated in both tests, RMET and MiniPONS, with no conclusive results. Some studies have found significant female superiority in RMET [32, 33], other investigations have found that females do not score significantly higher than males [eg. 23, 34–37]. Nevertheless, there are numerous investigations that show that women obtain significantly higher scores in tests that assess the ability to identify emotional facial expressions [38–41]. Performance in RMET decreases with age [42]. Regarding gender in MiniPONS performance, women achieve significantly better results than men [29], they process nonverbal emotional information more efficiently than men and obtain better scores in all channels [43]. With respect to the relationship between age and nonverbal sensibility, this ability declines with aging [43].

Evidence from family, twin and adoption studies indicates a heritable component to BD [44], suggesting a substantial genetic contribution to disease etiology and an elevated risk of developing BD [45]. If these deficits were the phenotypic expression of genetic vulnerability to BD, healthy subjects with a genetic predisposition to BD would be expected to display the

same deficits. Therefore, social cognitive dysfunction might be a possible endophenotype in BD. Research in social cognition of first-degree relatives of BD (FDR) is scant, there are findings that show that these individuals have a significant, but small impairment [46]. In this population, several different social cognitive tasks have been utilized across studies [47–49]. When measuring ToM in FDRs, with RMET, there are contradictory results. One study comparing offsprings with controls found significant deficits in this population [50]; another study did not find significant differences in unaffected adult FDRs of euthymic persons with BD [47]. Nonverbal sensitivity has not been measured in FDRs and only one study has been done with remitted BD, showing that these subjects performed significantly worse than the control group [51]. Given that the test MiniPONS has not been used before either with BDI or BD II population or with their first-degree relatives (comparing the three groups), this is an innovative aspect of this research. The aim of this study was to have a broader view of the difficulties of BDs and their families in the evaluation of ToM, assessing ToM with RMET and nonverbal sensitivity with MiniPONS, as useful measures of social cognition.

#### The present study

The objective of this research was to study first- degree relatives (FDR) of BD in a particular domain, social cognition, and compare their performance to that of two groups of remitted BDs (including not only a group of BD I, but also another group of BD II), and a control group. To the best of our knowledge, no previous studies explored performance of FDRs, comparing them with patients with BD II in ToM tasks, nor in nonverbal sensitivity. Among social cognition measures, a ToM test was chosen, the RMET, a tool that tests the ability to recognize emotional expressions and complex cognitive mental states. Theory of Mind in bipolar disorder has mostly been measured with the test RMET. As the RMET is based on facial static pictures, the objective was to complement this task with another dynamic tool of social cognition that presents scenes that are closer to real life situations, the MiniPONS, to explore their ability in the perception of different dynamic nonverbal channels as face, body movements and voice. The aim was to have a broad spectrum of family members' ability to recognize nonverbal cues, and to determine if BD I and BD II had worse performance than FDR. Specific hypotheses tested were: 1) social cognition deficits, measured with the two tests, are higher in patients with BD I or BD II than in FDR group; 2) when compared with healthy individuals without a family history of psychiatric disorders, results of FDRs are lower than those of the control group; 3) BD II participants do not have better results than BD I, and; 4) age and gender of participants affects the performance of all subjects; older participants and males perform worse in both tasks.

# Materials and methods

### Participants

The sample consisted of 154 persons: 37 FDRs of BD and, for comparison, 37 BD I, 40 BD II (both BD groups were in clinical remission) and 40 healthy controls. FDR and BD participants were recruited through self-help groups, and every FDR had only one first-degree biological sibling, offspring or parent who had a diagnosis of BD I or II. Collected data were age, gender, educational level, marital status, occupation, and diagnosis (BD I or BD II). The FDR sample comprised 37 individuals over the age of 25 (23 females and 14 males). Inclusion requirements criteria for the FDR group were: to have a first- degree familiar with a diagnosis of BD (I or II) and no current or past history of psychiatric or neurological illness, as well as no substance abuse. For BD groups, to enter the study, they should have been diagnosed with BD I or II and the requirement of having been euthymic at least during the previous three months.

	BDI I	(n = 37)	BD II	( <b>n</b> = 40)	FDR	(n = 37)	Control	(n = 40)	F	df	р
Age (Years)	44.73±12.81		49.88±11.47		51.03±13.51		48.53±13.84		1.738	3, 149	.162
Gender	n	%	n	%	n	%	n	%	$\chi^2$	df	р
Female	22	59.46	22	55.00	23	62.16	24	60	.274	3	.966
Male	15	40.54	18	45.00	14	37.84	16	40			
Medication BD	n	%	n	%					$\chi^2$	df	р
Lithium	19	51.35	13	33.33					2.812	1	.094
Anticonvulsant	14	37.83	23	58.97					2.976	1	.084
Antipsychotic	22	59.45	12	30.76					6.765	1	.009
Antidepressant	2	5.4	8	20.51					3.622	1	.057

#### Table 1. Demographic and clinical characteristics of the sample.

https://doi.org/10.1371/journal.pone.0246908.t001

BD is highly comorbid with addictions [52], Bipolar disorders are highly associated with alcohol use disorder [53], and generally, substance abuse is a major comorbidity in BD [54]. Lack of these two comorbidities was acknowledged in this study. Exclusion criteria for BD were as follows: patients with a (hypo)manic or depressive episode in the previous three months, alcohol abuse in the past six months or use of psychoactive substances during the same period. All BD I and BD II participants were receiving pharmacological treatment. Control group participants had no current or past psychiatric disorder. They were age and sex matched with FDR participants. Demographic characteristics are listed in Table 1.

#### **Ethical statement**

The study was approved by the Research Ethics Committee of Universidad Nacional de Educación a Distancia (Spain) and has been conducted according to the principles expressed in the Declaration of Helsinki. To participate, and after a thorough explanation of the study, all subjects provided written informed consent.

#### Measures

Following informed consent, and in order to verify the inclusion and exclusion criteria, the MINI Neuropsychiatric interview (in its Spanish adaptation) [55], was administered to FDR and BD groups. To confirm euthymia, absence of depressive and manic symptoms in BD, was measured with the Beck Depression Inventory II (BDI II) [56], in its Spanish version [57], and the Young Mania Rating Scale (YMRS) [58], in its Spanish adaptation [59].

The cut-off score in the scales to assess euthymia was  $\geq 30$  on the BDI II and  $\geq 7$  on the YMRS. In the Spanish adaptation for BDI II, for non-clinical and clinical Spanish populations, the cut-off scores would be equal to or higher than 19 and 30 respectively, inasmuch as those scores would show specificities over 90% and positive predictive values of 61% [60].

#### Social cognition assessment: ToM and nonverbal sensitivity

Two social cognition tasks were administered: the "Reading the Mind in the Eyes" (RMET) [23] to assess ToM, and the "MiniPONS" [29], to evaluate nonverbal sensitivity:

1. The Spanish version of the test RMET [61].

This tool involves examining 36 facial pictures and measures the ability to recognize what other people are thinking or feeling. The images consist of 36 grayscale photographs of the eye region of faces, of pictures that show only the eyes area of males and females (equal number of male and female faces) that reflect complex mental states and social emotions

(e.g., joking, surprised, contemplative). Below every photograph, there is a four-choice selection and the subjects have to choose one option (only one is the correct). 36 points is the highest score that can be achieved if all answers are correct. It has an approximate duration of 15 minutes, but there is no time limit to answer. A software application collects the stimuli and stores the responses. Reliability of this scale score for the present study was  $\alpha = .71$ .

2. The test MiniPONS in its Spanish version [43]. MiniPONS is a dynamic test that measures individual differences in the ability to recognize emotions, interpersonal attitudes and intentions, expressed through different nonverbal channels. MiniPONS consists in a set of short 64 video clips in black and white (plus three examples), that feature a woman with manipulated negative and positive emotional tone of facial expressions, body language, and voice. MiniPONS is composed by different expressive channels, in which all stimuli are grouped into a 2 x 2 design that combines affective valence and dominance: half of the stimuli show positive affect and the other half, negative. Similarly, half of the stimuli express dominant attitudes and the rest, submissive. It is administered through a computer application that presents the stimuli and records the responses (the total score). The response procedure is as follows: the video clip is present for two seconds, it disappears, and two possible answer options are shown in the screen. The participant must choose one of them, the one he thinks correct as to what the woman in the video is expressing. Once the subject has chosen the answer, the next video comes up. Total scores for each dimension were computed and reliability was near  $\alpha = .70$ .

#### Data analysis

The analysis performed to verify the endpoints of this study was a multiple linear regression analysis, to examine if social cognition differed among groups. Independent variables were group, gender and age, and dependent variables were the performance in the MiniPONS and RMET. To check if there was collinearity between predictors, several collinearity tests were computed. After checking that collinearity was non-significant, the independent variables were introduced in the model one-by-one, starting with the group, following by gender, and finally, age was the last variable included in the model. Significant level for all the regression analyses was .05. The analysis was carried out by means of R software [62].

#### Results

Descriptive statistics and regression analysis are shown in Tables 2 and 3 and Figs 1 and 2.

Regression analysis demonstrated that, in the RMET, FDRs results were significantly worse than those of the control group for the number of right answers variable, in the total score of this test, and BD II group had not better results than BD I. Age was negatively related to performance, and males made more mistakes than females in all groups. The percentage of associated variance was equal to 39.60%. In the MiniPONS, regression analysis showed that, in FDRs performance, there were not significant differences with control group. Patients with BD (I and II) had worse performance than controls in the number of correct responses achieved in this test. The percentage of associated variance was equal to 24.70%.

With respect to the MiniPONS channels, in the combined channel, there were no differences between FDRs and control group, and men scored lower than women (percentage of associated variance was equal to 7.20%). The same results, no differences between controls and FDRs, and men's lower scores, were found in the face-video (percentage of associated variance 25.50%), body-video (percentage of variance 11.50%), dominant (percentage of associated

Variable	Group	N	Mean	Median	SD	Min	Max	Skew	Kurt
MiniPONS Number of right answers	Control	40	48.93	49.00	3.68	43.00	55.00	-0.03	-1.30
	BD I	37	44.70	45.00	4.75	33.00	54.00	-0.23	-0.32
	BD II	40	44.88	44.50	4.79	33.00	55.00	-0.08	-0.28
	FDR	37	46.78	47.00	4.31	34.00	53.00	-0.78	0.42
Audio prosody channel	Control	40	11.37	11.00	1.71	9.00	15.00	0.44	-0.74
	BD I	37	10.70	11.00	2.15	3.00	14.00	-1.17	2.42
	BD II	40	11.00	11.50	1.89	6.00	15.00	-0.42	0.00
	FDR	37	11.51	12.00	1.95	7.00	15.00	-0.54	-0.51
Combined channel	Control	40	12.90	12.50	1.75	8.00	16.00	-0.38	0.03
	BD I	37	11.95	12.00	1.49	9.00	16.00	0.38	-0.14
	BD II	40	11.57	12.00	1.93	7.00	15.00	-0.38	-0.23
	FDR	37	12.22	12.00	1.86	8.00	15.00	-0.38	-0.36
Face video channel	Control	40	12.67	13.00	1.86	9.00	15.00	-0.42	-0.71
	BD I	37	11.32	12.00	1.80	8.00	15.00	0.05	-1.02
	BD II	40	11.28	11.00	1.72	8.00	15.00	-0.04	-0.45
	FDR	37	11.92	12.00	1.61	8.00	14.00	-0.54	-0.64
Body video channel	Control	40	12.00	12.00	1.91	9.00	15.00	-0.17	-1.12
	BD I	37	10.73	11.00	1.81	6.00	13.00	-0.71	-0.26
	BD II	40	11.03	11.00	1.85	6.00	14.00	-0.39	-0.40
	FDR	37	11.14	11.00	1.89	7.00	15.00	0.03	-0.49
Positive Valence	Control	40	24.77	26.00	2.75	20.00	29.00	-0.38	-1.22
	BD I	37	22.38	23.00	3.08	14.00	28.00	-0.50	-0.03
	BD II	40	22.55	22.50	2.79	17.00	28.00	0.25	-0.76
	FDR	37	23.43	24.00	2.62	17.00	29.00	-0.22	-0.37
Negative Valence	Control	40	24.17	24.50	2.42	20.00	29.00	-0.03	-1.05
	BD I	37	22.32	23.00	2.89	16.00	28.00	-0.22	-0.90
	BD II	40	22.32	23.00	3.13	16.00	28.00	-0.18	-0.53
	FDR	37	23.35	24.00	2.74	15.00	28.00	-0.63	0.25
Dominant	Control	40	24.37	24.50	2.06	21.00	28.00	0.16	-1.02
	BD I	37	22.16	22.00	3.05	12.00	27.00	-0.86	1.40
	BD II	40	22.32	22.50	3.36	13.00	29.00	-0.29	0.30
	FDR	37	23.70	24.00	2.63	15.00	28.00	-1.09	1.58
Submissive	Control	40	24.57	24.50	2.76	19.00	28.00	-0.38	-0.92
	BD I	37	22.54	23.00	2.74	16.00	28.00	-0.39	-0.38
	BD II	40	22.55	22.00	2.67	18.00	28.00	0.50	-0.68
	FDR	37	23.08	23.00	2.64	18.00	28.00	-0.33	-0.99
RMET: Total score	Control	40	29.23	29.00	2.80	22.00	35.00	-0.65	1.11
	BD I	37	22.41	22.00	3.94	12.00	30.00	-0.51	0.05
	BD II	40	23.05	24.00	4.55	11.00	32.00	-0.75	0.57
	FDR	37	25.54	25.00	3.80	18.00	33.00	0.18	-0.53

#### Table 2. Descriptive statistics.

Note. FDRs perform significantly worse than the control group in RMET.

https://doi.org/10.1371/journal.pone.0246908.t002

variance 14.80), submissive (percentage of associated variance 16.80%), positive (percentage of associated variance 20.30%) and negative valence (percentage of associated variance 12.10%) channels. BD groups (I and II) had worse results than controls and FDRs in all channels, except in the audio prosody channel (no differences between groups, age and gender).

Variable	Predictor	Estimate	95% CI	t	Р	$r_{adj}^2$	F	Р
MiniPONS Number of right answers	BD I	-4.570	(-6.421, -2.718)	-4.877	< .001	.109	7.228	< .001
	BD II	-3.531	(-5.333, -1.730)	-3.873	< .001			
	FDR	-1.865	(-3.700,030)	-2.008	.046			
	Gender	-2.068	(-3.398,739)	-3.074	< .001	.168	8.747	< .001
	Age	108	(160;055)	-4.060	< .001	.247	11.02	< .001
	Intercept	54.94	(52.047, 57.833)	37.53	< .001	-	-	-
Audio prosody channel	BD I	836	(-1.708, .035)	-1.897	.060	.014	1.706	.168
	BD II	505	(-1.352, .343)	-1.177	.241			
	FDR	013	(876, .850)	030	.977			
	Gender	263	(888, .362)	831	.407	.012	1.467	.215
	Age	003	(028, .022)	253	.801	.001	1.179	.322
	Intercept	11.787	(10.427, 13.148)	17.116	< .001	-	-	-
Combined channel	BD I	820	(-1.599,040)	-2.078	.004	.037	2.935	.035
	BD II	-1.061	(-1.819,303)	-2.675	.006			
	FDR	479	(-1.251, .294)	-1.225	.224			
	Gender	651	(-1.210,091)	-2.297	.023	.068	3.795	.006
	Age	013	(036, .008)	-1.249	.214	.072	3.359	.007
	Intercept	13.654	(12.437, 14.872)	22.158	< .001	-	-	-
Face video channel	BD I	-1.513	(-2.214,813)	-4.267	< .001	.072	4.957	.003
	BD II	-1.148	(-1.830,466)	-3.328	.001			
	FDR	597	(-1.292, .097)	-1.699	.092			
	Gender	637	(-1.140,134)	-2.503	.013	.117	6.045	< .001
	Age	054	(074,034)	-5.350	< .001	.255	11.46	< .001
	Intercept	15.504	(14.410, 16.599)	27.985	< .001	-	-	-
Body video channel	BD I	-1.400	(-2.211,589)	-3.412	< .001	.040	3.097	.029
	BD II	817	(-1.606,028)	-2.046	.043			
	FDR	776	(-1.580, .028)	-1.908	.058			
	Gender	518	(-1.099, .065)	-1.757	.081	.061	3.480	.009
	Age	037	(060,014)	-3.175	.002	.115	4.969	< .001
	Intercept	13.994	(12.727, 15.260)	21.827	< .001	-	-	-
Positive valence	BD I	-2.386	(-3.566, -1.205)	-3.992	< .001	.058	4.153	.007
	BD II	-1.603	(-2.752,454)	-2.757	.007			
	FDR	854	(-2.045, .316)	-1.443	.151			
	Gender	900	(-1.748,053)	-2.099	.038	.091	4.820	.001
	Age	080	(113,046)	-4.697	< .001	.203	8.814	< .001
	Intercept	28.691	(26.846, 30.536)	30.735	< .001	-	-	-
Negative valence	BD I	-2.184	(-3.417,951)	-3.501	< .001	.071	4.887	.002
-	BD II	-1.929	(-3.128,729)	-3.177	.002	]		
	FDR	-1.011	(-2.232, .211)	-1.635	.104	]		
	Gender	-1.168	(-2.053,283)	-2.608	.010	.112	5.811	< .001
	Age	028	(063, .007)	-1.599	.112	.121	5.209	< .001
	Intercept	26.249	(24.333, 28.175)	26.932	< .001	-	-	-

#### Table 3. Multiple linear regression in the prediction of the performance in MiniPONS and RMET tests.

(Continued)

Variable	Predictor	Estimate	95% CI	t	Р	$r_{adj}^2$	F	Р
Dominant	BD I	-2.187	(-3.467,906)	(-3.467,906) -3.375		.059	4.192	.007
	BD II	-1.596	(-2.841,350)	-2.531	.012			
	FDR	355	(-1.624, .914)	553	.581			
	Gender	-1.286	(-2.205,367)	-2.764	.006	.109	5.668	< .001
	Age	052	(088,015)	-2.815	.006	.148	6.330	< .001
	Intercept	27.185	(25.185, 29.186)	26.857	< .001	-	-	-
Submissive	BD I	-2.350	(-3.497, -1.203)	-4.049	< .001	.082	5.505	.001
	BD II	-1.898	(-3.017,781)	-3.356	.001			
	FDR	-1.475	(-2.613,337)	-2.562	.011			
	Gender	804	(-1.626, .019)	-1.930	.055	.107	5.534	< .001
	Age	057	(089,024)	-3.454	< .001	.168	7.140	< .001
	Intercept	27.750	(25.968, 29.533)	30.768	< .001	-	-	-
RMET: Total score	BD I	-7.368	(-9.022, -5.713)	-8.800	< .001	.348	28.270	< .001
	BD II	-6.217	(-7.827, -4.607)	-7.633	< .001			
	FDR	-3.881	(-5.521, -2.242)	-4.678	< .001			
	Gender	-1.400	(-2.588,213)	-2.331	.021	.373	23.750	<.001
	Age	062	(109,015)	-2.603	.010	.396	21.090	<.001
	Intercept	33.106	(30.522, 35.690)	25.314	<.001	-	-	-

#### Table 3. (Continued)

Note. CI: Confidence interval. Reference category for group = 'control'. Reference category for group = 'female'.

https://doi.org/10.1371/journal.pone.0246908.t003

### Discussion

This study investigated social cognition abilities in FDRs of BD as a risk for developing BD in this population. Two tools were used: RMET and MiniPONS. Consistent with the literature, the results supported the hypothesis that both BDs and their first-degree relatives had a deficit in social cognition. With regard to differences in social cognition between BD I and BD II, little research exists with respect to differences in social cognition between these two groups, inasmuch as most studies are carried out with BD I or mixed samples of BD I and BD II patients. Nevertheless, when they are explored with a ToM task, both groups seem to have similar impairments [22]. The second hypothesis of this study, predicting that BD II would not have better scores than BD I in both tests, was also confirmed: no significant differences in the results between BD I and BD II were found, both groups have the same impairment.



#### Fig 1. Differences between groups.

https://doi.org/10.1371/journal.pone.0246908.g001



#### Fig 2. Scatterplots: Role of group, sex and age in the study variables.

https://doi.org/10.1371/journal.pone.0246908.g002

With respect to the results in the positive valence channels of the MiniPONS, in the present study, BD groups had lower performance than control participants. Research exists that shows that BD is associated with persistently heightened positive emotional responses across contexts, compared with healthy controls [63, 64]. Gruber [65], studying BD I patients, found evidence that positive affect is more activated in this clinical group, comparing them with healthy population. In this study BD groups (I and II) and FDRs did not show this impairment, their performance in this variable was similar as that of the control group.

The results of this research showed that FRDs of BD, in the performance of the RMET, had a significant impairment in the recognition of complex mental states. FDRs performance was worse than that of control group and better than BDs (either type I or type II). However, with the test MiniPONS, no significant differences were found between FDRs and controls scores in this test. The results of this study showed that, RMET discriminated better between BDs (BD I and BD II groups) and their first-degree relatives, as BD familiars presented significative differences with controls in RMET, but not in MiniPONS. According to the expectations, the hypothesis predicting an intermediate performance of BD relatives between controls and BDs, was confirmed; they performed better than controls, but worse than BDs. These results could be understood as an empathy deficit of FDRs, that might have consequences for overall social functioning. This may negatively influence in the understanding of familiars diagnosed with BD and thus, have a repercussion in family relationships. This empathy deficit may be related to expressed emotion in FDR, that is, a measure of criticism, hostility and/or emotional overinvolvement in caregiving relatives when describing interactions with the patient [66, 67]. Deficits in social cognition may lead to impaired communication, and research has demonstrated that FDRs high expressed emotion communication is associated with risk of mood relapse among adults with BD [68-70]. This lack of understanding may also contribute to difficulties in maintaining adequate familial relationships, inasmuch as empathic skills are essential for successful social interactions [71]. Little research exists regarding differences in social cognition between BD II and BD II, inasmuch as most studies are carried out with BD I or mixed samples of BD I and BD II patients. Both groups seem to have similar impairments when they are explored with a ToM task [22]. We predicted that BD II would not have better scores than BD I in both tests, and this hypothesis was also confirmed. The prediction that male gender and age of participants would affect the performance of participants in both tests, was also confirmed in this study. Results showed that men and older participants (from all groups) obtained lower results in RMET and in most channels of MiniPONS.

The model of emotional competence [72]. emphasizes the importance of the ability to perceive emotional signals that facilitate the adaptation of the individual to constantly changing environments. Social cognitive abilities are crucial for effective interpersonal functioning. In this research, results show that FDRs were partially competent in the decoding of nonverbal signals, they were not very proficient in the understanding of other's internal states. Group psychoeducation in order to modify unproductive cycles of family interaction is a suggestion of some authors as Vieta [73]. One of the most relevant family interventions is that of Miklowitz et al. [67], who suggest the psychoeducational model as a type of psychosocial family intervention that may reduce the level of symptom severity or functional impairment. Family psychoeducation may increase families' abilities to diminish the number of relapses as well as to enhance BD patients' adherence to pharmacotherapy [74, 75]. In BD, possibly family therapy may be beneficial as adjuncts to pharmacological maintenance treatments [67]. Family Focused Treatment aims to reduce the high levels of stress and conflict in the families of bipolar patients, thereby improving the patient's illness course [76]. It has increased positive and decreased negative family communication, and BD patients who had parents who were negative, critical, or guilt-inducing in their interactions with the patient, had a 94% chance of having an illness recurrence in the 9 months after a hospitalization [67].

In the last years, in BD, the focus has also moved from clinical remission to functional recovery [77]. The concept of recovery, not only symptomatic (low scores on ratings of mania and depression that indicate near-absence of symptoms), but also functional recovery, is a goal to achieve in these patients. Thereby, psychosocial interventions with BD can directly help to prevent relapse, and social cognitive treatment to those with an actual diagnosis of bipolar disorder, may be desirable. Psychological treatments are cognitive-behavioral therapy, psychoeducation, interpersonal and social rhythm therapy, and family intervention [78]. A suggestion is, that treating BD disorder within a familial context, enhancing FDRs competences in social cognition abilities, in the inference of BDs internal states might increase the ability to identify communication conflicts due to a poor understanding of nonverbal signals. Adjunctive family interventions are beneficial on BD outcomes and caregivers well-being. Those interventions lead to decrease the patients' risk of recurrences and functional psychosocial impairment [79]. Group family therapy with FDRs of BD may include training in the recognition of nonverbal cues, which might help them to achieve a better understanding of their familiars with BD, in order to modify communication abilities. This competence, learning not to attribute nonverbal patient's behaviors as negative, may improve family relationships, a better management of their relatives with BD and acquisition of more positive patters of interaction.

Among the main limitations of this research, there is the fact that FDRs were not matched with the BDs participants. A future prospective may be to conduct a study with a FDR group, in which every individual could be matched with their familiar with BD. Another limitation is the women 's ratio in FDR group, that was higher than that of men, which leads to a possibility of a gender bias. There is also the fact that in the choice of social cognition tasks, in this research, RMET and MiniPONS were chosen, and there is a large number of available tasks that evaluate social cognition domains. Another limitation is the relatively small size of the sample, which could have reduced the significance of some results. Moreover, cognitive functioning of BDs has not been scored in this study. As a future prospect, in social cognition research, a suggestion is to measure the cognitive profile of BDs. In this research, all BD participants were medicated. If medication of BDs might have an influence on the results of this study, was not investigated, and establishing an impact of pharmacology on cognition in BD sample, is a complex issue. Confirmation of this will require further investigation.

# Conclusions

This research studied ToM and nonverbal sensitivity in FDR of BD. Two tasks were chosen, the RMET, a tool that tests the ability to recognize emotional expressions and complex cognitive mental states, and MiniPONS, a dynamic test that measures facial expressions, body language, and voice intonation. Results showed significative impairment in FDR in the ToM task, but not in nonverbal sensitivity, they did not perform better than BDs. A suggestion is that, treating BD disorder within a familial context, enhancing FDRs competences in social cognition abilities, may improve family relationships and a better management of their relatives with BD.

# **Supporting information**

**S1 Dataset.** (CSV)

# **Author Contributions**

Conceptualization: Enrique G. Fernández-Abascal.

Formal analysis: Mercedes Ovejero.

Investigation: Usue Espinós.

Methodology: Mercedes Ovejero.

Project administration: Enrique G. Fernández-Abascal.

Resources: Usue Espinós.

Supervision: Enrique G. Fernández-Abascal, Mercedes Ovejero, Guillermo Lahera.

Visualization: Guillermo Lahera.

Writing - original draft: Usue Espinós.

#### References

- 1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.
- Judd LL, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry.2005; 62(12): 1322–30. https://doi.org/10.1001/archpsyc. 62.12.1322 PMID: 16330720
- Rosa AR, et al. Functional impairment in bipolar II disorder: Is it as disabling as bipolar I? Journal of Affective Disorders.2010; 127: 71–76. https://doi.org/10.1016/j.jad.2010.05.014 PMID: 20538343
- Altshuler LL, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J. Clin. Psychiatry.2006; 67: 1551– 1560. https://doi.org/10.4088/jcp.v67n1009 PMID: 17107246
- Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. Bipolar Disord.2005; 7: 281–285. https://doi.org/10.1111/j.1399-5618.2005.00207.x PMID: 15898966
- Depp CA, et al. Social competence and observer-rated social functioning in bipolar disorder. Bipolar Disord.2010; 12(8): 843–850. https://doi.org/10.1111/j.1399-5618.2010.00880.x PMID: 21176031
- Sierra P, Livianos L, Rojo L. Quality of life for patients with bipolar disorder: relationship with clinical and demographic variables. Bipolar Disord.2005; 7(2): 159–165. https://doi.org/10.1111/j.1399-5618.2005. 00186.x PMID: 15762857
- MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr Scand.2001; 103(3): 163–170. <u>https://doi.org/10.1034/j.1600-0447.2001.00059.x</u> PMID: <u>11240572</u>

- Tohen M et. al. Two Year Syndromal and Functional Recovery in 219 Cases of First- Episode Mayor Psychiatric Disorder With Psychotic Features. Am J Psychiatry.2000; 157(2): 220–228. https://doi.org/ 10.1176/appi.ajp.157.2.220 PMID: 10671390
- Kessler RC, et al. The prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. Am J Psychiatry.2006; 163(9): 1561–1668. <u>https://doi.org/10. 1176/ajp.2006.163.9.1561</u> PMID: 16946181
- Schulze TG, et al. Further evidence for age of onset being an indicator for severity in bipolar disorder. J Affect Disord.2002; 68(2–3): 343–345 https://doi.org/10.1016/s0165-0327(01)00306-8 PMID: 12063163
- Gamage N, Senanayake S, Kumbucage M, Mendis J, Jayasekara A. The prevalence of anxiety and its association with the quality of life and illness severity among bipolar affective disorder patients in a developing country. Asian Journal of Psychiatry.2020; 52: 102054. <u>https://doi.org/10.1016/j.ajp.2020</u>. 102044 PMID: 32344280
- Vázquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview Depress Anxiety.2014: 31(3), 196–206. https://doi.org/10.1002/da.22248
- Köhler-Forsberf O, et al. Familial severe psychiatric history in bipolar disorder and correlation with disease severity and treatment response. J Affec Disord.2020; 273: 131–137. https://doi.org/10.1016/j. jad.2020.03.157
- Post RM, et al. Multigenerational positive family history of psychiatric disorders is associated with a poor prognosis in bipolar disorder. J Neuropychiatr Clin Neurosci.2015; 27(4): 304–310. https://doi.org/ 10.1176/appi.neuropsych.14080204 PMID: 26258489
- Samamé C, Martino DJ, Strejilevich S. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. Acta Psychiatrica Scandinavica.2012; 125(4): 266–280. <u>https://doi.org/ 10.1111/j.1600-0447.2011.01808.x PMID: 22211280</u>
- Baez S, Herrera E, Villarin L, Theil D, Gonzalez-Gadea ML, Gomez P. Contextual Social Cognition Impairments in Schizophrenia and Bipolar Disorder. PLoS ONE.2013: 8(3): e57664. <u>https://doi.org/10.1371/journal.pone.0057664</u>
- Frith CD. Social cognition. Philos Trans R Soc London B Biol Sci.2008; 363(1499): 2033–2039. <a href="https://doi.org/10.1098/rstb.2008.0005">https://doi.org/10.1098/rstb.2008.0005</a> PMID: 18292063
- Premack D, Woodruff G. Does the chimpanzee have a theory of mind? Behavioral and Brain Sciences. 1978; 4: 51–526. http://doi.org/10.1017/S0140525X00076512
- Derntl B, Seidel EM, Kryspin-Exner I, Hasmann A, Dobmeier M. Facial emotion recognition in patients with bipolar I and bipolar II disorder. British Journal of Clinical Psychology.2009:48(4): 363–375. <u>https:// doi.org/10.1348/014466509X404845</u> PMID: 19220936
- Benito A, Lahera G, Herrera S, Muncharaz R, Benito G, et al. Deficits in recognition, identification, and discrimination of facial emotions in patients with bipolar disorder. Rev Bras. Psiquiatr.2013; 35(4). http://doi.org/10.1590/1516-4446-2013-1086
- Martino DJ, Strejilevich SA, Fassi G, Marengo E, Igoa A. Theory of mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders. Psychiatry Research.2011; 189(3): 379–384. <u>https://doi.org/10.1016/j.psychres.2011.04.033</u> PMID: 21620484
- Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. J Child Psych Psychiatry 2001; 42(2): 241–251. https://dx.doi.org/10.1111/1469-7610.00715
- Cusi A, MacQueen, GM. McKinnon MC. Patients with bipolar disorder show impaired performance in complex test of social cognition. Psychiatry Res.2012; 200(2–3): 258–264. <u>https://doi.org/10.1016/j.psychres.2012.06.021</u> PMID: 22854176
- Espinós U, Fernández-Abascal EG, Ovejero M. What your eyes tell me: Theory of mind in bipolar disorder. Psychiatry Res 2018; 262: 536–41. https://doi.org/10.1016/j.psychres.2017.09.039 PMID: 28969860
- Ibanez A, Urquina H, Petroni A, Baez S., Lopez V, do Nascimento, et al. Neural Processing of Emotional Facial and Semantic Expressions in Euthymic Bipolar Disorder (BD) and its Association with Theory of Mind (ToM). PLoS One. 20127(10): e46877. http://dx.doi.org/10.1371/journal.pone.0046877
- Thaler NS, Allen D, Sutton, NP, Vertinski M, Ringdahl EN. Differential impairment of social cognition factors in bipolar disorder with and without psychotic features and schizophrenia. J Psychiatr Res.2013; 47: 2004–2010. https://doi.org/10.1016/j.jpsychires.2013.09.010 PMID: 24112946
- Hall JA, Roter DL, Blanch DC, Frankel RM. Nonverbal Sensitivity in Medical Students: Implications for Clinical Interactions. J Gen Intern Med.2009; 24(11): 1217–1222. https://doi.org/10.1007/s11606-009-1107-5 PMID: 19771481

- Bänziger T, Scherer KR, Hall JA, Rosenthal R. Introducing the MiniPONS: A Short Multichannel Version of the Profile of Nonverbal Sensitivity (PONS). J Nonverb Behav.2011; 35(3): 189–204. <u>http://dx.doi.org/10.1007/s10919-011-0108-3</u>
- 30. De Gelder B. Why bodies? Twelve reasons for including bodily expressions in affective neuroscience. Philosophical Transactions of The Royal Society B Biological Sciences.2009; 364(1535): 3475–3484. https://doi.org/10.1098/rstb.2009.0190 PMID: 19884142
- Dael N, Mortillaro M, Scherer KR. Emotion expression in body action and posture. Emotion.2012; 12 (5): 1085–1101. https://doi.org/10.1037/a0025737 PMID: 22059517
- Alaerts K, Nackaerts E, Meyns P, Swinnen SP, Wenderoth N. Action and Emotion Recognition from Point Light Displays: An Investigation of Gender Differences. Plos One.2011; 6 (6): e20989. https://doi. org/10.1371/journal.pone.0020989 PMID: 21695266
- Vellante M, Baron-Cohen S, Melis M, Marrone M, Petretto DR, Masala C, et al. The "Reading the Mind in the Eyes" test: Systematic review of the psychometric properties and a validation study in Italy. Cognitive Neuropsychiatry.2013; 18(4): 326–354. https://doi.org/10.1080/13546805.2012.721728
- Baron-Cohen S, et al. The "Reading the Mind in the Eyes" Test: Complete Absence of Typical Sex Difference in ~400 Men and Women with Autism. Plos One.2015; 10(8): e0136521. <u>https://doi.org/10.1371/journal.pone.0136521 PMID: 26313946</u>
- **35.** Chapman E, Baron-Cohen S, Auyeung B, Knickmeyer R, Taylor K, Hacket G. Fetal testosterone and empathy: evidence from the empathy quotient (EQ) and the "Reading the Mind in the Eyes" test. Social Neuroscience.2006; 1:135–148. https://doi.org/10.1080/17470910600992239 PMID: 18633782
- Cook CM, Saucier DM. Mental rotation, targeting ability and Baron-Cohen's Empathizing\_Systemizing Theory of Sex Differences. Personality and Individual Differences.2010; 49: 712–716. <u>https://doi.org/ 10.1016/j.paid.2010.06.010</u>
- Kettle JWL, O'Brien-Simpson L, Allen NB. Impaired theory of mind in first episode schizophrenia: Comparison with community, university and depressed controls. Schizophr Res.2008; 99: 96–102. https:// doi.org/10.1016/j.schres.2007.11.011 PMID: 18155447
- Collignon O, Girard S, Gosselin F, Saint-Amour D, Lepore F, Lassonde M. Women process multisensory emotion expressions more efficiently than men. Neuropsychologia.2010; 48(1): 220–225. <u>https://</u> doi.org/10.1016/j.neuropsychologia.2009.09.007 PMID: 19761782
- Baron-Cohen S, Wheelwright S. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. Journal of Autism and Developmental Disorders.2004; 34: 163–175. https://doi.org/10.1023/b:jadd.0000022607.19833.00 PMID: 15162935
- Hall JA, Matsumoto D. Gender Differences in Judgments of Multiple Emotions From Facial Expressions. Emotion.2004; 4(2): 201–206. https://doi.org/10.1037/1528-3542.4.2.201 PMID: 15222856
- Hampson E, vanAnders SM, Mullin LI. A female advantage in the recognition of emotional facial expressions: test of an evolutionary hypothesis. Evolution and Human Behavior.2006; 17(6): 401–416. <a href="https://doi.org/10.1016/j.evolhumbehav.2006.05.002">https://doi.org/10.1016/j.evolhumbehav.2006.05.002</a>
- 42. Kynast J, et al. Mindreading From the Eyes Declines With Aging–Evidence From 1,603 Subjects. Front. Aging Neurosci, 2020. | https://doi.org/10.3389/fnagi.2020.550416
- Martínez-Sánchez F, Fernández-Abascal EG, Martínez-Modia JC. Adaptación española de la versión reducida multicanal del Perfil de Sensibilidad No Verbal (MiniPONS). Anales de Psicología.2013; 29 (2): 604–613. http://doi.org/10.6018/analesps.29.2.161851
- Craddoc N, Jones I. Genetics of bipolar disorder. Journal of Medical Genetics. 1999; 36(8): 585–594. https://doi.org/10.1136/jmg.36.8.585 PMID: 10465107
- Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. American Journal of Medical Genetics.2003; 123C(1): 48–58. https://doi.org/10.1002/ajmg.c.20013 PMID: 14601036
- Bora E, Ozerdem A. Social cognition in first-degree relatives of patients with bipolar disorder: a metaanalysis. European Neuropsychopharmacologie.2017; 27(4): 293–300. <u>https://doi.org/10.1016/j.</u> euroneuro.2017.02.009
- Reynolds MT, Van Rheenen TE, Rossell SL. Theory of mind in first degree relatives of individuals with bipolar disorder. Psychiatry Res.2014; 219: 400–402. https://doi.org/10.1016/j.psychres.2014.05.041 PMID: 24947917
- Santos JM, Pousa E, Soto E, Comes A, Roura P, et al. Theory of Mind in Euthymic Bipolar Patients and First-Degree Relatives. Journal of Nervous and Mental Disorders.2017; 205: 207–212. <u>https://doi.org/ 10.1097/NMD.00000000000595</u> PMID: 27660998
- 49. Whitney J, Howe M, Shoemaker V, Li S, Sanders EM, Dijamco C, et al. Socio-emotional processing and functioning of youth at high risk for bipolar disorder. J Affect Disord.2013; 148(1): 112–117. <u>https:// doi.org/10.1016/j.jad.2012.08.016</u> PMID: 23123133

- Maróthi R, Kéri S. Intuitive physics and intuitive psychology ("theory of mind") in offspring of mothers with psychoses. Peer J 2014(1); [e330]. https://doi.org/10.7717/peerj.330 PMID: 24749009
- Espinós U, Fernández-Abascal EG, Ovejero M. Theory of mind in remitted bipolar disorder: Interpersonal accuracy in recognition of dynamic nonverbal signals. PLoS ONE.2019; 14(9): e0222112. https:// doi.org/10.1371/journal.pone.0222112 PMID: 31509553
- Cerullo MA, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. Subst. Abuse Treat. Prev. Policy, 2(29) (2007), p. 29. https://doi.org/10.1186/1747-597X-2-29 PMID: 17908301
- Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: systematic review and meta-analysis. J Affect Disord.2016; 206: 331–349. https://doi.org/10.1016/j.jad.2016.07.011 PMID: 27476137
- Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Lafiti S. Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry Research.2017; 253: 338–350. https://doi.org/10.1016/j.psychres.2017.02.067 PMID: 28419959
- 55. Ferrando L, Bobes J, Gibert, J, Soto M, Soto O. MINI: Entrevista Neuropsiquiátrica Internacional. Versión en Español 5.0.0. DSM-IV 2000. Traducida por L. Franco-Alfonso, L. Franco. Retrieved from http:// entomologia.rediris.es/pub/bscw/cgi/d602335/MINI/Entrevista Neuropsiquiátrica Internacional.pdf
- Beck AT, Steer RA, Brown GK. BDI-II. Beck Depression Inventory-Second Edition manual. San Antonio, TX: The Psychological Corporation.1996.
- 57. Sanz J, Perdigón AL, Vázquez C. Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): 2. Propiedades psicométricas en población general. Clínica y Salud.2003; 14(3): 249–280. Retrieved in: http://www.redalyc.org/articulo.oa?id=180617972001. Matched ISSN: 1130-5274
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. The Br J Psychiatry.1978; 133(5): 429–435. https://doi.org/10.1192/bjp.133.5.429 PMID: 728692
- 59. Colom F, Vieta E, Martínez-Arán A, García-García M, Reinares M, Torrent C, et al. Versión española de una escala de la evaluación de la manía: Validez y fiabilidad de la escala de Young. Medicina Clínica 2002; 119: 366–371. https://doi.org/10.1016/s0025-7753(02)73419-2 PMID: 12372167
- 60. Sanz J. 50 años de los inventarios de depresión de Beck: Consejos para la utilización de la adaptación española del BDI II en la práctica clínica. Papeles del Psicólogo. 2013; 34(3): 161–68. <u>http://www.papelesdelpsicologo.es</u> ISSN 0214–7823
- Fernández-Abascal EG, Cabello R, Fernández-Berrocal P, Baron-Cohen S. Test-retest-reliability of the "Reading the Mind in the Eyes Test": a one year follow up study. Molecular Autism.2013; 4: 33. <u>https://doi.org/10.1186/2040-2392-4-33 PMID: 24020728</u>
- R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.2019; URL: http://www.r-project.org/index.html
- Gruber J. Can Feeling Too Good Be Bad? Positive Emotion Persistence (PEP) in Bipolar Disorder. Curr Dir Psychol Sci.2011; 20(4): 217–221. https://doi.org/10.1177/0963721411414632
- Gruber J, Harvey AG, Purcell AL. What goes up can come down? A preliminary investigation of emotion reactivity and emotion recovery in bipolar disorder. J of Affect Disorders.2011; 133: 457–466. <u>https://</u> doi.org/10.1016/j.jad.2011.05.009
- Gruber J, Siegel EH, Purcell AL, Earls HA, Cooper G, Barrett LF. Unseen positive and negative affective information influences social perception in bipolar I disorder and healthy adults. J Affect Disord.2016; 192: 191–198. https://doi.org/10.1016/j.jad.2015.12.037 PMID: 26745436
- Jindal RD, Thase ME. Integrating psychotherapy and pharmacotherapy to improve outcomes among patients with mood disorders. Psychiatr Serv.2003; 54(11): 1484–90. <u>https://doi.org/10.1176/appi.ps.</u> 54.11.1484 PMID: 14600307
- Miklowitz DJ, Chung B. Family-Focused Therapy for Bipolar Disorder: Reflections on 30 Years of Research. Family Process.2016; 55(3): 483–499. <u>https://doi.org/10.1111/famp.12237</u> PMID: 27471058
- Kim EY, Miklowitz DJ. Expressed emotion as a predictor of outcome among bipolar patients undergoing family therapy. J Affect Disorders.2004; 82(3): 343–352. <u>https://doi.org/10.1016/j.jad.2004.02.004</u> PMID: 15555685
- Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, et al. Familyfocused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry.2000; 48(6): 582–592. <u>https://doi.org/10.1016/s0006-3223(00)00931-8 PMID: 11018229</u>
- 70. Yan LJ, Hammen C, Cohen, AN, Daley, SE, Henry RM. Expressed emotion versus relationship quality variables in the prediction of recurrence in bipolar patients. J Affect Disord.2004; 83(2–3): 199–206. https://doi.org/10.1016/j.jad.2004.08.006 PMID: 15555714

- Whittle S, Yücel M, Yap MBH, Allen NB. Sex differences in the neural correlates of emotion: Evidence from neuroimaging. Biological Psychology.2011; 87(3): 319–333. <u>https://doi.org/10.1016/j.biopsycho.</u> 2011.05.003 PMID: 21600956
- Scherer KR. The dynamic architecture of emotion: Evidence for the component process model. Cognition & Emotion.2009; 7: 1307–1351. http://doi.org/10.1080/02699930902928969
- 73. Vieta E, Colom F. Psychological interventions in bipolar disorder: From wishful thinking to an evidencebased approach. Acta Psychiatr Scand.2004; 110: 34–38. <u>https://doi.org/10.1111/j.1600-0447.2004.</u> 00411.x
- 74. Miklowitz DJ. A review of evidence-based psychosocial interventions for bipolar disorder. Journal of Clinical Psychiatry. 2006; 67(Suppl 11); 28–33. PMID: 17029494
- Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR. Psychosocial interventions for the prevention of relapse in bipolar disorder: systematic review of controlled trials. Br J Psychiatry.2008; 192 (1): 5–11. https://doi.org/10.1192/bjp.bp.107.037887 PMID: 18174500
- 76. Miklowitz DJ. The Role of the Family in the Course and Treatment of Bipolar Disorder. Curr Dir Psychol Sci.2007; 16(4):192–196. https://doi.org/10.1111/j.1467-8721.2007.00502.x PMID: 18185847
- 77. Vieta E, Torrent C. Functional remediation: the pathway from remission to recovery in bipolar disorder. World Psychiatry.2016; 15: 288–289. https://doi.org/10.1002/wps.20351 PMID: 27717267
- Reinares M, Sanchez-Moreno J, Fountulakis K. Psychosocial interventions in bipolar disorder: What, for whom and when. J Affective Disorders. 2014; 156: 46–55. https://doi.org/10.1016/j.jad.2013.12.017
- **79.** Reinares M, Bonnin CM, Hidalgo-Mazzei D, Sanchez-Moreno J, Colom F, Vieta E. The role of family interventions in bipolar disorder: A systematic review. Clinical Psychology Review.2016; 43: 47–57. https://doi.org/10.1016/j.cpr.2015.11.010 PMID: 26691629